

REMARKS

I. Status Summary

Claims 1-14 and 36-38 are now pending in the subject U.S. patent application and have been examined.

Claims 1-3, 6-9, and 36-38 remain rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over McMahan et al. (236 *Anal Biochem* 101-106, 1996; hereinafter "McMahan") or the Product Information for MOLECULAR PROBES™ PRO-Q™ Oligohistidine Blot Stain Kit #2 dated September 27, 2001 (hereinafter "the PRO-Q™ Product Information") in view of Neville et al. (6 *Prot Sci* 2436-2445, 1997; hereinafter "Neville") and Nieba et al. (252 *Anal Biochem* 217-228, 1997; hereinafter "Nieba"). Claims 1, 2, 4, and 6-14 remain rejected under this section upon the contention that the claims are unpatentable over the 1996 Ph.D. Dissertation of Gholam Ehteshami (hereinafter the "Ehteshami Dissertation") in view of Neville and Nieba.

Claim 37 has been canceled.

Claims 35 and 36 have been amended. The amendment to withdrawn claim 35 is to correct a typographical error in which the first listed step of the method was not given a letter. Support for the amendments to claim 36 can be found throughout the specification as filed, including particularly in the claims as originally filed. More particularly, claim 36 has been amended to independent form to include all of the elements of the claim from which it depended (*i.e.*, claim 1) and further to include the element recited in claim 37, and thus the amendments to claim 36 are supported by claims 1 and 37. Accordingly, applicants respectfully submit that no new matter has been added by the amendments to the claims.

New claim 39 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in the claims as originally filed. More particularly, new claim 39 find support in claim 2 as originally filed and on page 9, lines 15-16 of the specification as filed.

Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Summary of Telephone Interview Dated July 18, 2006

A telephone interview was conducted on July 18, 2006. Participating in the interview were Examiner Brandon J. Fetterolf of the United States Patent and Trademark Office (hereinafter "the Patent Office") and applicants' representative Christopher P. Perkins. Discussed during the interview were the art-based rejections over Nieba and the Ehteshami Dissertation.

Applicants' representative suggested an alternative interpretation of Nieba and a structural interpretation of the Ehteshami Dissertation that were asserted to distinguish the claims over these references. While agreement was not reached concerning these interpretations during the interview, applicants were invited to develop these points more fully in this response, which applicants respectfully submit that they have done hereinbelow. Applicants would like to thank Examiner Fetterolf for his time and efforts in discussing the issues presented in the Official Action.

III. Response to the First Obviousness Rejection

Claims 1-3, 6-9, and 36-38 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over McMahan or the PRO-Q™ Product Information in view of Neville and Nieba. According to the Patent Office, these references disclose the following:

1. McMahan

- (a) a conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety;
- (b) that the chelator is NTA, the metal is Ni²⁺, and the detectable moiety is biotin; and
- (c) the conjugate further comprises a spacer between the chelator-ion moiety and the detectable label, and that the conjugate is soluble in aqueous solution.

2. The PRO-Q™ Product Information

- (a) conjugate of formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety;

- (b) chelator is NTA, metal is Ni^{2+} , and the detectable moiety is biotin; and
- (c) a kit comprising the conjugate, a secondary reagent for detecting the conjugate, and instructions for using the kit.

3. Nieba

- (a) that while typically Ni^{2+} , Zn^{2+} , Co^{2+} , and Cu^{2+} are conjugated to NTA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag.

4. Neville

- (a) Fe^{3+} -loaded NTA preferentially binds to phosphopeptides as compared to His-containing peptides.

Based on these assertions, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art to substitute Ga^{3+} or Fe^{3+} as taught by Neville in view of Nieba. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants respectfully submit that in Nieba, the choice of metal ion is ubiquitously based on the affinity to proteins that contain a His tag. There is no teaching or suggestion in Nieba that the metal ion can influence binding to any protein that does not have a His tag, and in fact, Nieba teaches that the metal ion can be chosen so that binding to proteins that do not have His tags can be reduced or eliminated. Accordingly, it is axiomatic that any "optimization" of Nieba results in improved selectivity and/or affinity for a protein with a His tag. Modifications that would result in decreased affinity and selectivity for a His tag-labeled protein are clearly not optimizations of Nieba. One does not optimize by destroying the intended functionality.

The Patent Office is thus believed to be misconstruing the "optimization" taught in Nieba because the optimizing only relates to eliminating non-specific binding, not to enhancing desirable binding to some other moiety. This is clear from the citation from Nieba referred to on page 4 of the instant Official Action. Page 217, 2nd column, 1st paragraph states the following: "the choice of the metal ion and buffer conditions for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag, which does not necessarily give the tightest binding of the His tag" (emphasis

added). In other words, Nieba only discloses that the metal ion and the buffer conditions can be manipulated such that the degree of binding to polypeptides that have the His tag versus the degree of non-specific binding to polypeptides that do not have the His tag is optimized.

Therefore, applicants respectfully submit that the Patent Office's assertion that Nieba would have motivated one of ordinary skill in the art to substitute the metal ion taught by McMahan or the PRO-Q™ Product Information to produce a metal chelate that recognizes other proteins, such as phosphoproteins, that do not contain a His tag finds no support in Nieba. The Patent Office's assertion that Nieba teaches that changing the metal ion can produce chelates that bind to new moieties is clearly in error, since Nieba teaches that changing the metal ion is intended to reduce non-specific binding. A more likely interpretation is that Nieba teaches away from the chelation of proteins that are not identifiable by a His tag, such as phosphoproteins.

The Office Action also asserts that Applicants' arguments involving lack of motivation to combine the references are against the references individually, where the rejection is based on the combination of references. This *non sequitur* is based on the assumption that a *prima facie* case of obviousness has already been made. Applicants respectfully remind the Examiner that three criteria must be met to establish a prima facie case of obviousness: (1) there must be motivation to modify the reference or combine teachings; (2) there must be a reasonable expectation of success; and (3) the reference (or combination thereof) must teach or suggest all the claim limitations. Accordingly, for the purposes of establishing a *prima facie* case of obviousness, one cannot combine references without motivation and a reasonable expectation of success. Applicants have provided ample evidence to show that there is no motivation to combine the references, and in fact, they teach away from concomitant use.

Accordingly, applicants respectfully submit that contrary to the Patent Office's assertions, Nieba does not provide one of ordinary skill in the art with any motivation to combine McMahan and the PRO-Q™ Product Information with the other references because the disclosure of Nieba relates only to eliminating binding of proteins that do not contain His tags. Thus, applicants respectfully submit that there is no motivation to combine the McMahan reference and the PRO-Q™ Product Information with Nieba and

Neville. Indeed, there is believed to be particularly no motivation to provide a detection reagent for phosphoproteins that is soluble in aqueous medium as presently recited in claim 2 and newly added claim 39.

Thus, it is respectfully submitted that the Patent Office has not presented a *prima facie* case of obviousness of claims 1-3, 6-9, 36, and 38 over the combination of these references. Applicants therefore respectfully request that the instant rejection be withdrawn at this time.

IV. Response to the Second Obviousness Rejection

Claims 1, 2, 4, and 6-14 have been rejected under 35 U.S.C. § 103(a) upon the contentions that the claims are unpatentable over the Ehteshami Dissertation in view of Neville and Nieba. The Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville in view of Nieba to produce a metal chelate that recognizes other proteins such as phosphoproteins. The Patent Office further asserts that one of ordinary skill in the art would have been motivated to modify the references because Nieba teaches that the choice of metal ion for IMAC can be optimized for the highest selectivity relative to other proteins not carrying a His tag.

Applicants respectfully submit that the remarks presented hereinabove are equally applicable to the instant rejection. Particularly, applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine Neville and the Ehteshami Dissertation because the Patent Office's assertions with respect to the disclosure of Nieba are based on a misinterpretation of Nieba as discussed hereinabove. Thus, applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine the Ehteshami Dissertation with Neville and Nieba. Indeed, there is believed to be particularly no motivation to provide a detection reagent for phosphoproteins that is soluble in aqueous medium.

Furthermore, applicants respectfully submit that the various moieties found in the affinity reagents disclosed in the Ehteshami Dissertation have different functions than they do in the instantly claimed subject matter, and as such, if these affinity reagents

were modified to contain Ga^{3+} or Fe^{3+} , would not function as phosphoprotein detection reagents.

For example, applicants respectfully submit that the Ehteshami Dissertation appears to disclose heterobifunctional polyethylene glycols. Particularly, the Ehteshami Dissertation appears to disclose biotin-PEG-iminodiacetic acid-copper conjugates for purifying avidin. As shown in Figure 1.2 of the Ehteshami Dissertation, a chelating matrix coordinating a metal ion is bound to a solid support. The metal ion is also coordinated by a PEG derivative comprising a bioligand. This bioligand moiety functions in the disclosed PEG derivatives as the ligand that binds to the protein of interest, while the coordinated metal ion links the PEG derivative to the chelating matrix attached to the solid support. Thus, in the heterobifunctional polyethylene glycols disclosed in the Ehteshami Dissertation, the chelator-metal ion moiety binds to the PEG derivative.

This is in stark contrast to the chelator-metal ion moiety present in the phosphoprotein detection reagent (PPDR) of claim 1. Applicants respectfully submit that section (ii) of claim 1 and section (d) of claim 10 clearly recite that the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein. As a result, even if one of ordinary skill in the art were motivated to replace the copper ion in the heterobifunctional polyethylene glycols disclosed in the Ehteshami Dissertation with Ga^{3+} or Fe^{3+} , the resulting chelator-metal ion moieties would still bind to the PEG derivative. In the Ehteshami Dissertation, it is the bioligand moiety and not the chelator-metal ion moiety that binds to the ligand of interest, and as such, applicants respectfully submit that the affinity reagents disclosed therein are structurally and functionally different than the PPDRs of claims 1 and 10.

In response to applicants' arguments presented in the previous Amendment, the Patent Office asserts that the Ehteshami Dissertation teaches that aqueous two-phase partitioning in conjunction with metal affinity and specific affinity partitioning using heterobifunctional polymers can be used as a tool for distinguishing and screening of specific binding sites on the surface of proteins (*citing* page 145, 2nd paragraph). Thus, the Patent Office asserts that the heterobifunctional bispecific chelate polymer has the same function as the instantly claimed PPDRs of claim 1. Applicants respectfully submit that this assertion finds no support in the Ehteshami Dissertation. Notably, the

heterobifunctional bispecific chelate polymers disclosed in the Ehteshami Dissertation bind to proteins by virtue of their bioaffinity ligands. Claim 1 recites in subsection (b) that the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein.

As such, applicants respectfully submit that even assuming *arguendo* that the heterobifunctional bispecific chelate polymers disclosed in the Ehteshami Dissertation do have the same general function as the presently disclosed PPDRs (*i.e.*, binding to moieties found on proteins), the individual components of the PPDRs of the presently disclosed subject matter have different structures and functions. Therefore, the Patent Office's assertion that the Ehteshami Dissertation supports the instant rejection appears to be an example of the Patent Office considering just the "gist" of the claimed subject matter in violation of M.P.E.P. § 2141.02.

Accordingly, applicants respectfully submit that claims 1 and 10 have been distinguished over the combination of the Ehteshami Dissertation and Neville in view of Nieba. Claims 2, 4, 6-9, and 11-14 all depend directly or indirectly from claim 1 or claim 10, and thus are also believed to be distinguished over the cited combination. Therefore, applicants respectfully request that the instant rejection of claims 1, 2, 4, and 6-14 be withdrawn. Applicants further respectfully submit that claims 1, 2, 4, and 6-14 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V. Discussion of the New Claim

New claim 39 has been added. Support for the new claim can be found throughout the specification as filed, including particularly in the claims as originally filed. More particularly, new claim 39 find support in claim 2 as originally filed and on page 9, lines 15-16 of the specification as filed.

New claim 39 is believed to be distinguishable from the combinations cited by the Patent Office against the currently pending claims for the reasons set forth hereinabove. Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claim 36 over the combination of McMahan or the PRO-Q™ Product Information in view of Neville and Nieba, and thus claim 39, which depends from claim 36, is also believed to be distinguished over this combination.

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CONCLUSIONS

In accordance with the amendments to the claims and the remarks presented hereinabove, applicants respectfully submit that claims 1-4, 6-14, 36, 38, and 39 are now in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, Examiner Fetterolf is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

Deposit Account

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,

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